
Epigenetic Priming of Enhancers Predicts Developmental Competence of hESC-Derived Endodermal Lineage Intermediates.

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Public Summary:

The potential to generate functional pancreatic beta cells or liver cells from human embryonic stem cells provides a promising avenue for cell replacement therapies for treatment of diabetes and chronic liver disease, respectively. Despite progress, beta cells and liver cells produced from stem cells still lack many of the characteristics of normal human beta or liver cells. Pancreas and liver arise from a common precursor cell and organ specific-inductive signals must act upon these precursor cells to activate either pancreas- or liver-specific genes. However, the molecular mechanisms controlling pancreas versus liver fate decisions are not understood. Here, we employed a human embryonic stem cell (hESC) differentiation system toward pancreas and liver to examine if cell fate decisions could be determined by the state of enhancers: regulatory DNA sequences that, when bound by transcription factors, enhance gene transcription. We show that pancreas- and liver-specific enhancers of these precursor cells are in a "poised" state for activation. When precursor cells are exposed to inductive factors, this leads to rapid changes in the chromatin structure of these enhancers. These changes render the cell competent to appropriately respond to inductive signals by allowing accessibility of the DNA to lineage-specifying transcription factors and activation of either pancreas- or liver-specific genes. The findings discussed in this work have implications for cell reprogramming strategies to produce beta cells and liver cells from other cell sources.

Scientific Abstract:

Embryonic development relies on the capacity of progenitor cells to appropriately respond to inductive cues, a cellular property known as developmental competence. Here, we report that epigenetic priming of enhancers signifies developmental competence during endodermal lineage diversification. Chromatin mapping during pancreatic and hepatic differentiation of human embryonic stem cells revealed the en masse acquisition of a poised chromatin state at enhancers specific to endoderm-derived cell lineages in gut tube intermediates. Experimentally, the acquisition of this poised enhancer state predicts the ability of endodermal intermediates to respond to inductive signals. Furthermore, these enhancers are first recognized by the pioneer transcription factors FOXA1 and FOXA2 when competence is acquired, while subsequent recruitment of lineage-inductive transcription factors, such as PDX1, leads to enhancer and target gene activation. Together, our results identify the acquisition of a poised chromatin state at enhancers as a mechanism by which progenitor cells acquire developmental competence.

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